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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,286	12/07/1999	MICHAEL GROLL	P564-9039	3782

7590 05/28/2004

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EXAMINER	
CLOW, LORI A	

ART UNIT	PAPER NUMBER
1631	26

DATE MAILED: 05/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,286	GROLL ET AL.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 27 June 2003, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 28-36 are currently pending. Claims 1-27 have been cancelled.

Claim Rejections - 35 USC § 112

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-30 and 32-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *This is a new grounds of rejection.*

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or

absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must be able to identify and isolate proteasome inhibitors based upon some crystallized fraction of a cell extract. However, for the reasons discussed below, this constitutes undue experimentation.

b) and c) The specification provides examples for known proteasomes in the art, such as the 20S proteasome from *Archaebacterium Thermoplasma acidophilum* (page 1, 3rd paragraph) and the eukaryotic proteasome, 20S, from *Sacchromyces cerevisiae* (page 2, 2nd paragraph). Many other examples from the art are given on pages 3-5. The specification goes on to describe that the identification and isolation of new proteasome inhibitors is carried out using a computer-aided modeling programs such as INSIGHT for determining the accessible volumes for ligands at active sites. Identification of ideal ligand properties is carried out by programs such as LUDI and electronic properties on surfaces may be determined by programs such as GRASP (page 7, beginning line 23-page 8, line 5). However, the instant claims do not include computer-aided modeling steps and are therefore not enabled for identifying an inhibitor. Claim 1 requires steps for obtaining cells, lysing cells, separating extracts, testing extracts for activity, crystallizing samples, and analyzing the structure to identify new proteasomes. One of skill in the art would not know how to go from the step of analyzing to identification of inhibitors without additional steps that include computer modeling such as outlined in the specification without undue experimentation.

Furthermore, the specification provides working examples of protein preparations from *Saccharomyces cerevisiae* (page 11, example 1) only. The specification also provides crystallization procedures and analysis techniques pertaining to yeast, but not to the myriad of other proteasomes potentially encompassed by the instant claims.

d) The invention is drawn to methods of finding proteasome inhibitors using crystal data. However, the instant specification indicates that computer modeling be used to carry out the invention. The step of "analyze" provides no guidance as to what to model for in order to find supposed inhibitors of proteasomes. In claims 30, 32, and 33 the structure analysis of the crystallized fractions is done by comparison of the data to known proteasomes structures. However, according to the specification, no proteasomes from eukaryotes have been crystallized and prokaryotic proteasome homology is too low (page 2). Therefore, would more complex starting materials of other known eukaryotics lead to the same purity of fractions using the steps in the instant claims?

In addition, the specification indicates at page 13 that the crystal were immersed in an inhibitor solution after the fractionations and crystallization. However, the instant claims do not include that step. If only active fractions are isolated and crystallized then analyzed, how can an inhibitor be identified, absent that step?

e) and g) It would have been well known in art that crystallization of eukaryotic proteasomes is difficult, at best. The specification outlines the difficulties in the prior art for obtaining purity for crystallization of eukaryotic proteasomes (beginning at page 1). For example, Morimoto et al. (J. Biol. Chem. (1995) Vol. 117, pages 471-474) isolate proteasomes from bovine liver and the preparation was purified on hydroxyapatite, as in the instant invention.

Morimoto et al. were unable to determine the structure due to low purity and modeling could not be accomplished. The instant specification indicates that the instant invention has overcome the problems associated with purification in the prior art, however the fact remains that identification of a proteasome inhibitor is not possible without the steps of molecular modeling in the claims.

f) The skill of those in the art of crystallography is high.

h) The claims are broad because they do not elucidate how identification of an inhibitor would be performed.

The skilled practitioner would first turn to the instant specification for guidance to practice these methods. However, the instant specification does not provide specific guidance to practice these embodiments. As such, the skilled practitioner would turn to the prior art for such guidance, however, the prior art shows that such predictions are highly unpredictable, and require substantial additional work and research. Finally, said practitioner would turn to trial and error experimentation to determine identify proteosome inhibitors. Such represents undue experimentation.

Written Description

Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 36 is a reach through claim and is not described in the specification as filed. The specification does not describe an inhibitor that is identified by the method. The fact that one

could identify an inhibitor does not overcome the fact that one would have no knowledge beforehand of the inhibitor, unless disclosed in the specification as filed. Applicant must show possession of the claimed invention by describing the claimed invention with all of its limitations. However, the instant specification does not meet this requirement.

112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "analyzing the structure of the resulting crystals". It is unclear how the analysis is being performed. Analysis could mean any number of techniques, such as x-ray diffraction, electron microscopy, or determination of 3-D coordinates, for example.

Claim 30 is vague and indefinite because it is unclear from where or from what the crystal data comes? Is the proteasome pocket S1 of the subunits indicated from yeast or from mammal or from some other eukaryote? It is unclear how a proteasome pocket from one species could be the same in another species.

Claim 32 is vague and indefinite because it is unclear how modification of the crystal structure data of a yeast proteasome is performed. How does one modify this data with amino acid sequences from the human proteasome?

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242, or (703) 308-4028.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Legal Instrument Examiner, Tina Plunkett, whose telephone number is (703) 305-3524, or to the Technical Center receptionist whose telephone number is (571) 272-0549.

MARJORIE MORAN
PATENT EXAMINER

Marjorie A. Moran
5/26/04

May 26, 2004

Lori A. Clow, Ph.D.
Art Unit 1631
Lori A Clow